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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/672,429

Applicant(s)

DEMPCY ET AL.

Examiner

John S. Brusca

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 110-127 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 110-127 is/are rejected.
- 7) ☒ Claim(s) 110, 111, 114, 119, 121 and 126 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

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DETAILED ACTION

1. This Office action contains new grounds of rejection under 35 U.S.C. 101 and 103(a) not necessitated by the applicant's amendment and is therefore a nonfinal Office action.

Status of the Claims

2. Claims 110-127 are pending.

Claims 110-127 are rejected.

Claims 110, 111, 114, 119, 121 and 126 are objected to.

Priority

3. The applicants claim for priority filed 28 February 2008 has been entered. The benefit of priority to application numbers 09/640953, 09/054832, 09/431385, and 09/054830 is not granted relevant to the instant claimed subject matter because the applications do not fulfill the requirements of 35 U.S.C. 112, first paragraph regarding nearest neighbor analysis. Therefore the granted priority date for the instant claimed subject matter is that of application no. 09/724959, 28 November 2000.

Terminal Disclaimer

4. The terminal disclaimer filed on 04 August 2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Application No. 10/176,972 has been reviewed and is accepted. The terminal disclaimer has been recorded.

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Claim Objections

5. Claims 110, 111, 114, 119, 121(in the list of structures and in the last section) and 124 are objected to because of the following informalities: The claims list members of a group without a comma between the last two members of the group, making the number of members of the group unclear . Appropriate correction is required.
6. Claim 126 is objected to for recitation of “wherein said oligonucleotide an enhanced ability” and should be amended to recite “wherein said oligonucleotide has an enhanced ability.”

Claim Rejections - 35 USC § 101

7. Claims 110-127 are rejected under 35 U.S.C. 101 because these claims are drawn to non-statutory subject matter.

Claims 110-127 are drawn to a process. A process is statutory subject matter under 35 U.S.C. 101 if: (1) it is tied to a particular machine or apparatus or (2) it transforms an article to a different state or thing (In re Bilski, 88 USPQ2d 1385 Fed. Cir. 2008).

The claimed subject matter is not limited to a particular apparatus or machine. To qualify as a statutory process, the claims should require use of a machine within the steps of the claimed subject matter or require transformation of an article to a different state or thing. Insignificant extra-solution activity in the claimed subject matter will not be considered sufficient to convert a process that otherwise recites only mental steps into statutory subject matter. Preamble limitations that require the claimed process to comprise machine implemented steps will not be considered sufficient to convert a process that otherwise recites only mental steps into statutory

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subject matter. The applicants are cautioned against introduction of new matter in an amendment.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 110-127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 110-123, 126, and 127 are indefinite because it is not clear if a molecule (an oligonucleotide) or data of a sequence of an oligonucleotide are required in the first stem of claims 110 and 111. Step a) of claims 110 and 111 recite “providing an oligonucleotide” which in the art refers to a molecule, however the remaining steps of the method are limited to data manipulation. It is not clear how the recited molecule could be used in the steps of the method.

Claims 124 and 125 are indefinite because the claims from which they depend do not appear to require the presence of physical molecules, as noted above, but the claims state that the oligonucleotides are used in hybridization procedures or are part of an array apparatus.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 110, 112, 113, 118, 123, and 124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutz et al. (Biotechniques Vol. 27, pages 1218-1224 (1999), reference 65 in the Information Disclosure Statement filed 25 February 2004) in view of Martin et al. (Nucleic Acids Research Vol. 13, pages 8927-8938 (1985) in view of Loakes et al. Nucleic Acids Research Vol. 23, pages 2361-2366 (1995).

The instant claims are drawn to a computer mediated process of predicting and outputting to a display the melting temperature of an oligonucleotide sequence by calculating the nearest neighbor thermodynamic parameters for each of the N-1 neighboring base pairs in the identified sequence, wherein the identified sequence includes at least one universal base. In some embodiments the oligonucleotide sequence is derived from the GenBank database, the melting

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temperature is predicted with an accuracy of about 2 degrees Celsius, and conditions for hybridization are established.

Schutz et al. teach a computer-mediated method for calculating T_m of input oligonucleotide sequences that is implemented in a standard PC running Microsoft Windows and Excel and shows an output window display in figure 3 of calculated melting temperatures. Schutz et al. discloses a spreadsheet software (i.e. processing module that returns the T_m of the identified oligonucleotide sequence) for thermodynamic melting point prediction of oligonucleotide hybridization with and without mismatches in the abstract and throughout. Schutz et al. shows inputting the oligonucleotide sequence from the GenBank database in the second column of page 1219. Schutz et al. shows that the method predicts the melting temperature of the input oligonucleotide sequence with an accuracy of 2.4 degrees Celsius in the second column of the next to last page and figure 4. Schutz et al. shows that the method aids hybridization-probe experiments by allowing the melting temperature to be estimates accurately on the next to last page. The method of Schutz et al. uses the nearest neighbor thermodynamic parameters wherein a single base pair binding is influenced by the surrounding base pairs (page 1218, right column, lines 8-30, and page 1219, left column, last paragraph, and in the Formulas and Equations section on page 1224).

Schutz et al. does not show calculating the thermodynamic parameters for an oligonucleotide sequence that includes a least one modified base that is a universal base.

Martin et al. shows that deoxyinosine can be used as a component in oligonucleotides that hybridizes with approximately equal thermodynamic parameters to all bases in a hybridizing

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oligonucleotide (see the abstract and Tables 1-4, and the discussion on pages 8937. On page 8927 Martin et al. note that the nucleotide deoxyinosine comprises the base hypoxanthine. Martin et al. determines the nearest neighbor thermodynamic parameters for deoxyinosine at permuted positions in an oligonucleotide on pages 8930-8932 and Tables 2-4. Martin et al. states on page 8937 that deoxyinosine is useful to produce oligonucleotides that have reduced specificity to target oligonucleotides.

Loakes et al. states on page 2361 that universal bases are useful for manipulating DNA in vitro, and that hypoxanthine is one of the few characterized bases that can be used as a universal base. Loakes et al. shows oligonucleotides that comprise deoxyinosine (and consequently the deoxyinosine associated base hypoxanthine) in Table 1, figure 1, and the discussion on the first column of page 2363. Loakes et al. states that primers comprising deoxyinosine can be used to prime polynucleotide synthesis by a polymerase if the proper templates are chosen.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the computer mediated method of Schutz et al. by allowing for use of deoxyinosine, which is shown by Loakes et al. to be a universal base, because Martin et al. performs nearest neighbor analysis for deoxyinosine and shows that it has utility for production of oligonucleotides that hybridize with reduced specificity. Integration of deoxyinosine in the method of Schutz et al. would require routine substitution of thermodynamic nearest neighbor parameters for deoxyinosine as shown in Martin et al. into the program of Schutz et al.

12. Claims 110-113, 118-121, 123, and 124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to

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claims 110, 112, 113, 118, 123, and 124 above, and further in view of Kutyaivin et al. '97 (Nucleic Acids Research Vol. 25, pages 3718-3723 (1997)).

The claims are drawn to a computer mediated method of predicting the melting temperature of an oligonucleotide sequence comprising a universal base and a minor groove binder.

Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above do not show oligonucleotides with minor groove binders.

Kutyaivin et al. '97 shows oligonucleotides with attached minor groove binders in the abstract and throughout. Kutyaivin et al. '97 shows that minor groove binders increase the binding affinity of oligonucleotides, see tables 1 and 3. Kutyaivin et al. '97 shows oligonucleotides comprising deoxyinosine and minor groove binders on pages 3721-3722 and table 4, and shows that the addition of minor groove binders dramatically increases the stability and melting temperature of the deoxyinosine containing oligonucleotides. Kutyaivin et al. '97 shows the structure of the minor groove binder claimed in claim 121 in figure 1. Kutyaivin et al. '97 shows quantitative data for the increase in melting temperature conferred by the minor groove binder in tables 1-4. Kutyaivin et al. '97 concludes on page 3722 that minor groove binders have the advantage of increasing the melting temperature of oligonucleotides without decreasing the specificity of the oligonucleotides when binding a sequence specific target oligonucleotide.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Schutz et al. in view of Martin et al. in view of

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Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above by predicting the melting temperature of oligonucleotides that comprise minor groove binders because Kutayav in et al. '97 determines the quantitative increase that minor groove binders confer on oligonucleotide melting temperature and shows that oligonucleotides with minor groove binders have the advantage of increasing stability without decreasing sequence specificity when oligonucleotides bind a target sequence.

13. Claims 110, 111, 114, 116, 117, and 127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above, and further in view of Singh et al. (cited as reference 68 in the Information Disclosure Statement filed 25 February 2004, Chemical Communications pages 455-456 (1998), a copy has been entered into the instant application file).

The claims are drawn to a computer mediated method of predicting the melting temperature of an oligonucleotide sequence comprising a universal base and a locked sugar. In some embodiments the oligonucleotides have improved mismatch discrimination.

Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above do not show an oligonucleotide sequence comprising a universal base and a locked sugar.

Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above do not show oligonucleotides with a locked sugar.

Singh et al. shows oligonucleotides comprising locked sugars in the abstract and throughout. Singh et al. shows in Tables 1 and 2 the quantitative increase in melting temperature

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of oligonucleotides and in the discussion on page 456 concludes that oligonucleotides with locked sugars have improved mismatch discrimination.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of the method of Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above by predicting the melting temperature of oligonucleotides that comprise locked sugars because Singh et al. determines the quantitative increase that locked sugars confer on oligonucleotide melting temperature and shows that oligonucleotides with locked sugars have the advantage of improved mismatch discrimination.

14. Claims 110, 111, 114, and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above, and further in view of Griffin et al. (Analytical Biochemistry Vol. 260, pages 56-63 (1998))

The claims are drawn to a computer mediated method of predicting the melting temperature of an oligonucleotide sequence comprising a universal base and a peptide nucleic acid backbone.

Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above do not show an oligonucleotide sequence comprising a universal base and a peptide nucleic acid backbone.

Griffin et al. disclose a method for calculating the duplex stability and melting temperature of nucleic acids comprising a peptide nucleic acid backbone using nearest neighbor

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models (see the abstract and pages 57-59). Griffin et al. disclose that their average difference between calculated and measured duplexes was 2.2 degrees. Griffin et al. states that peptide nucleic acids have advantages of higher stabilities when hybridized to DNA than does the corresponding DNA:DNA hybrid, and that peptide nucleic acids have higher stabilities in low ionic strength conditions.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of the method of Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above by predicting the melting temperature of oligonucleotides that comprise a peptide nucleic acid background because Griffin et al. shows nearest neighbor analysis of oligonucleotides with peptide nucleic acid backbones and shows that peptide nucleic acid backbones have an advantage of higher stabilities when hybridized to DNA than does the corresponding DNA:DNA hybrid, and that peptide nucleic acids have higher stabilities in low ionic strength conditions.

15. Claims 110, 111, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above, and further in view of Lizardi et al. (U.S. Patent No. 6,403,319).

The claims are drawn to a computer mediated method of predicting the melting temperature of an oligonucleotide sequence comprising a universal base wherein the oligonucleotide is on an array.

Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above do not show an oligonucleotide on an array.

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Lizardi et al. discloses capture probes in the form of detector probes that are used to capture other nucleic acid molecules (column 10, lines 60-61). Lizardi et al. further disclose that these probes can contain modified nucleotides (column 11, lines 31-33). Lizardi et al. disclose that the duplex stability of these probes can be calculated using a variety of methods including those using nearest-neighbor models (column 12, lines 51- 53, see the Santa Lucia reference cited therein).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above by using the oligonucleotide on an array because Lizardi et al. shows that oligonucleotides may be used for hybridization assays when on an array.

16. Claims 110, 119, 120, 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above, and further in view of Kutyavin et al. '00 (Nucleic Acids Research Vol. 28 pages 655-661, cited in the Office action mailed 14 September 2006)

The claims are drawn to a computer mediated method of predicting the melting temperature of an oligonucleotide sequence comprising a universal base wherein the oligonucleotide comprises a minor groove binder linked by a quencher molecule.

Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above do not show an oligonucleotide comprising a minor groove binder linked by a quencher molecule.

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Kutyavin et al. '00 shows oligonucleotides comprising a minor groove binder linked by a quencher molecule termed TAMRA on 656. Kutyavin et al. shows in the abstract and pages 656-659 and figure 6 that the oligonucleotides have improved mismatch discrimination and higher melting temperatures.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above by the addition of minor groove binders that are linked by a quencher molecule because Kutyavin et al. '00 shows that such oligonucleotides have the advantage of higher melting temperature and improved mismatch discrimination.

17. Claims 110, 111, 114, 115, and 126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above, and further in view of Griffin et al. as applied to claims 110, 111, 114, and 115 above, and further in view of Kutyavin et al. '00.

The claims are drawn to a computer mediated method of predicting the melting temperature of an oligonucleotide sequence comprising a universal base wherein the oligonucleotide comprises a peptide nucleic acid backbone and a minor groove binder linked by a quencher molecule.

Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above, and further in view of Griffin et al. as applied to claims 110,

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111, 114, and 115 above do not show an oligonucleotide comprising a minor groove binder linked by a quencher molecule.

Kutyavin et al. "00 shows oligonucleotides comprising a minor groove binder linked by a quencher molecule termed TAMRA on 656. Kutyavin et al. shows in the abstract and pages 656-659 and figure 6 that the oligonucleotides have improved mismatch discrimination and higher melting temperatures.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Schutz et al. in view of Martin et al. in view of Loakes et al. as applied to claims 110, 112, 113, 118, 123, and 124 above, and further in view of Griffin et al. as applied to claims 110, 111, 114, and 115 above by the addition of minor groove binders that are linked by a quencher molecule because Kutyavin et al. "00 shows that such oligonucleotides have the advantage of higher melting temperature and improved mismatch discrimination.

Double Patenting

18. The provisional rejection of claims 110-116 and 118-121 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 6-9 of copending Application No. 10/176,972 in the Office action mailed 30May 2008 is withdrawn in view of the terminal disclaimer filed 04 August 2008.

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Conclusion

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John S. Brusca/

Primary Examiner

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